IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Randolph J. Noelle et al.

Application No.: 09/849,969 Confirmation No.: 1327

Filed: May 8, 2001 Art Unit: 1644

For TREATMENT OF T CELL MEDIATED IMMUNE DISORDERS Examiner: P. Gambel

APPEAL BRIEF

Mail Stop: Appeal Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Appellant's Appeal Brief under 37 C.F.R. § 41.37 is submitted in support of their appeal from the Panel Decision of the Pre-Appeal Brief Review dated December 6, 2007 in this patent application.

In accordance with the Pre-Appeal Brief Conference Pilot Program, "[t]he time period for filing an appeal brief will be reset to be one month from mailing of the decision on the request, or the balance of the two-month period running from the receipt of the notice of appeal, whichever is greater." Because the Panel Decision was mailed December 6, 2007, and the Notice of Appeal was filed October 17, 2007, Appellant submits that he is entitled to one month from the mail date of the Panel Decision to file the present Appeal Brief with no extension fees (*i.e.*, filing due by January 6, 2008). Therefore, Appellant submits that this Appeal Brief is timely filed. However, the Commissioner is hereby authorized to charge any fees deemed required in connection with this Appeal Brief, or to credit any overpayment, to Deposit Account No. 04-0100.

I. Real party in interest

The real party in interest is the Trustees of Dartmouth College, the owner of this application by assignment recorded at the United States Patent and Trademark Office on December 29, 1997, at Reel 8884, Frame 0777. The assignment was recorded in parent application serial no. 08/481,755, which issued into U.S. Patent No. 5,833,987.[1]

II. Related appeals and interferences

There are no appeals, interferences or judicial proceedings known to the Appellant or its legal representatives which may be related to, directly affect or that would have any bearing on the Board's decision in the pending appeal.

III. Status of claims

Claims 1, 5-10, 17, and 19 are pending, rejected, and are being appealed. Claims 2-4, 11-16, 18, and 20-21 have been cancelled. Claims 1-21 are attached hereto in the "Claims Appendix."

IV. Status of amendments

A final Office Action was transmitted on February 7, 2007. An Amendment and Response pursuant to 37 C.F.R. 1.116 was submitted to the United States Patent and Trademark Office on April 9, 2007. In an Advisory Action mailed May 9, 2007, the Examiner entered the claim amendments for the purposes of appeal, but stated that the Applicant's arguments did not place the claims in condition for allowance.

On June 20, 2007, a Pre-Appeal Brief Request for Review was submitted in accordance with the Pre-Appeal Brief Conference Program together with a Notice of Appeal.

[1] The Netherlands Health Organization was also recorded as an assignee on the same date and on the same reel and frame as assigned by co-inventor Eric Classen. Mr. Classen was removed as an inventor due to an amendment to the claims made May 9, 2003. The deletion of Mr. Classen as an inventor was recognized in an Office Action mailed July 24, 2003. Thus, the Netherlands Health Organization is presently not an assignee or a party in interest.

However, a Request for Continued Examination (RCE) was filed in the application on July 10, 2007 along with an Information Disclosure Statement and references.

A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on July 18, 2007 stating that the Pre-appeal Brief Request was improper due to the filing of the RCE. On September 20, 2007, the Examiner issued a second final Office Action rejecting claims 1, 5-10, 17, and 19. In response, on October 17, 2007, a second Pre-Appeal Brief Request for Review was submitted in accordance with the Pre-Appeal Brief Conference Program together with a Notice of Appeal.

A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on December 6, 2007, wherein the Panel: (1) determined that the application remains under appeal because there is at least one actual issue for appeal; and (2) maintained the rejection of claims 1, 5-10, 17, and 19.

V. Summary of claimed subject matter

The currently claimed invention is a method for preventing T cell mediated tissue destruction associated with type I diabetes comprising administering to a subject in need of such treatment a prophylactically effective amount of a gp39 antagonist selected from the group consisting of soluble CD40, CD40 fusion protein, and an anti-gp39 antibody, or a fragment thereof that binds gp39, wherein the anti-gp39 antibody is produced by 24-31 hybridoma, ATCC Accession Number HB 11712, and tissue destruction results from a T cell mediated immune reaction to an autoantigen (claim 1; specification, page 2, lines 14-20; page 2, lines 38-39; page 3, lines 7-13; page 3, lines 15-22; page 3, lines 31-36; page 4, lines 4-6; page 4, lines 9-17; page 5, lines 11-18; page 6, lines 19-25).

In a preferred embodiment, the gp39 antagonist is an anti-gp39 antibody (claim 5; specification, page 4, lines 12-13; page 4, line 20-page 6, line 40). In a further embodiment, the anti-gp39 antibody is a monoclonal antibody (claim 6; specification, page 4, line 40-page 5, line 10; page 6, lines 15-25), and a preferred anti-gp39 monoclonal antibody is deposited 24-31 (claim 8; specification, page 6, lines 19-25). The anti-gp39 antibody can also be an anti-human gp39 antibody (claim 7; page 6, lines 15-25).

The anti-gp39 monoclonal antibody can also be a chimeric monoclonal antibody containing constant regions and variable regions from different species (claim 9; specification, page 6, lines 26-35) or a humanized monoclonal antibody (claim 10; specification, page 5, line 35-page 6, line 5). The chimeric monoclonal anti-gp39 antibody can comprise a variable region of monoclonal antibody 24-31 (claim 17; specification, page 6, lines 30-36) and the humanized monoclonal anti-gp39 antibody can comprise a hypervariable region of monoclonal antibody 24-31 (claim 19; specification, page 5, line 35-page 6, line 5; page 6, lines 34-36).

VI. Grounds of rejection to be reviewed on appeal

The sole ground for rejection on appeal is whether claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Lederman *et al.* (U.S. Patent No. 6,592,868) ("Lederman"), in view of Noelle (U.S. Patent No. 5,747,037) ("Noelle").

VII. Argument

A. Rejection of Claims 1, 5-10, 17, and 19 under 35 U.S.C. § 103, as obvious over Lederman in view of Noelle

Claims 1, 5-10, 17, and 19

The Examiner improperly rejects claims 1, 5-10, 17, and 19, as obvious over the combination of Lederman with Noelle. He contends that Lederman, which teaches the use of a CD40L-specific antibody for the treatment of diabetes, in combination with the disclosure of the 24-31 antibody in Noelle, renders the currently claimed method obvious.

In order to make a showing of obviousness, the Examiner must make the four factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17-18 (U.S. 1966): (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations, such as long felt need, commercial success, and unexpected results. *See KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1734, 167 L.Ed.2d 705, 715 (2007). In considering obviousness, "[t]he proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all of the facts."

Examination Guidelines for Determining Obviousness under 35 U.S.C 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed Reg. 72 (195), pages 57526-57535 at 57528, quoting 35 U.S.C. § 103(a). As shown below, the claimed invention is not obvious because the differences between the prior art and the claims on appeal are too great to render the claims obvious, and one of skill in the art would have not considered the claimed invention obvious. Additionally, the Examiner has not properly considered the evidence of unexpected results that is of record in this application.

The present claims call for a method of preventing *T cell mediated tissue destruction associated with type I diabetes* comprising the administration of a gp39 antagonist, wherein the *tissue destruction results from a T cell mediated immune reaction to an autoantigen.* It is this prevention of T cell mediated tissue destruction resulting from a T cell mediated, *i.e.*, cellular, immune reaction to an autoantigen that is not taught or suggested in either Lederman or Noelle, alone or combined. Without an express or suggested teaching of these claim limitations in the prior art references, one of skill in the art would not have considered the claimed method obvious based upon their disclosure because at the time it was not known that gp39/CD40L had any role in non-B cell mediated immune responses. Additionally, the use of a gp39 antagonist to prevent T cell mediated tissue destruction associated with type I diabetes where the tissue destruction is caused by a T cell mediated immune response to an autoantigen was an unexpected and surprising result in view of the knowledge and skill in the art at the time of the filing of the application.

To prove the state of the art and provide evidence of unexpected results, Appellant submitted the Declaration of Edward A. Clark, Ph.D. (hereafter "Clark Declaration") with the Amendment and Response dated November 6, 2006. It is respectfully submitted that the Examiner did not give adequate consideration to this evidence as it establishes that after consideration of all of the facts, the method defined in the claims on appeal would not have been obvious to a person of skill in the art.

In summary, the present claims are not obvious over the combined teachings of Lederman and Noelle because:

(1) unlike the claims on appeal which cover a method of preventing T cell mediated tissue destruction resulting from T cell mediated immune responses by administering a gp39 antagonist, Lederman teaches only the inhibition of B cell mediated immune responses by the administration of a CD40L antagonist, and teaches only a method of treating diabetes by inhibition of B cell mediated immune responses, not T cell mediated responses;

(2) Noelle teaches only the administration of a gp39 antagonist in conjunction with a antigen or antigen presenting cell to induce antigen specific T cell tolerance in an organ transplant or graft versus host disease. Unlike the claims on appeal, there is no disclosure in Noelle of the claim limitations of administering a gp39 antagonist alone to prevent T cell mediated, *i.e.*, cellular, tissue destruction associated with type I diabetes caused by a T cell mediated immune reaction to a self antigen, independent of B cell activation;

(3) there would have been no motivation to combine Lederman and Noelle because Lederman is concerned with the use of a gp39 antagonist alone to treat B cell mediated autoimmune disorders and Noelle teaches the use of a gp39 antagonist administered with an antigen or antigen presenting cell to inhibit immune responses to donor antigens. There is no description or suggestion in Noelle to modify the method described therein to exclude the administration of donor antigen or donor antigen-expressing cells for the purpose of achieving an inhibition of a response to self, such as in autoimmune disorders. Moreover, there would have been no expectation of success in achieving the presently claimed invention by combining the teachings of Lederman and Noelle;

(4) the state and knowledge of the art in June of 1995 was such that without an express or suggested teaching of the use of a CD40L antagonist to inhibit T cell mediated immune reactions that cause T cell mediated tissue destruction associated with diabetes, one of skill in the art would not have considered the currently claimed invention obvious because it was not known that gp39/CD40L had any involvement in T cell mediated immune responses independent of B cell activation; and

(5) the ability of a gp39 antagonist to prevent T cell mediated tissue destruction associated with type I diabetes, wherein the tissue destruction results from a T cell mediated

immune reaction to an autoantigen was an unexpected and surprising result in view of the state of the art in June of 1995. Additionally the superior results of the antibody 24-31 in the claimed method was also surprising and unexpected in view of the disclosure of the 5c8 antibody in Lederman.

1. Lederman does not Disclose or Suggest the Currently Claimed Invention

As stated above, the currently claimed invention calls for a method for preventing *T cell mediated tissue destruction associated with type I diabetes* comprising the administration of a gp39 antagonist, *wherein the tissue destruction results from a T cell mediated immune reaction to an autoantigen*. Despite the Examiner's assertions, Lederman does not teach or suggest claims to a method of preventing T cell mediated tissue destruction, and his teachings are limited to treating B cell immune responses, as shown by the passage at column 10, line 62 to column 11, line 7 (emphasis added):

> This invention provides a *method of inhibiting B cell activation* to an animal which comprises administering to the animal an effective inhibiting amount of a pharmaceutical composition comprising the monoclonal antibody which specifically recognizes the activated T cell surface protein and a pharmaceutically acceptable carrier. For the purposes of this invention, an "effective inhibiting amount" of a pharmaceutical composition is any amount of the pharmaceutical composition which is effective to bind to a protein on the surface of the activated T cells and thereby *inhibit T cell activation of B cells*. In one embodiment of this invention, the B cells are resting B cells. In another embodiment of this invention, the B cells are primed B cells.

Moreover, there is nothing in Lederman that would expand the scope of his disclosure beyond a method of inhibiting B cell activation. In fact, Lederman discloses only that CD40L antagonists target helper T cell/ B cell interactions, not T cell mediated immunological responses. *See* Clark Declaration, ¶ 18. For example, Lederman presents data in Figure 11 showing that CD40L is not expressed on CD8+ T cells, which are the T cells responsible for T cell mediated responses. Additionally, Lederman states that "[t]he monoclonal antibody

described and claimed herein binds to *T cell which are interacting with B cells* in the germinal centers of lymph nodes and *not to other T cells*." Lederman, col. 6, ll. 65-67 (emphasis added). Lederman also states that "[f]or the purposes of this invention 'activated T cells' are T cells capable of providing T cell helper function to resting B cells." Lederman, col. 7, ll. 6-8. Moreover, the cell line used in Lederman, D1.1, is described as a T cell "capable of constitutively providing contact-dependent helper function to B cells." Lederman, col. 9, ll. 4-9. These statements establish that Lederman discloses only B cell mediated responses and that T cells only function is to provide help to B cells. There is no teaching or suggestion in Lederman of inhibiting T cell mediated immune responses as claimed, only B cell mediated responses. Clark Declaration, ¶ 19. Thus, Lederman does not disclose or suggest the method of the claims on appeal for preventing the T cell mediated tissue destruction associated with type I diabetes, where the tissue destruction results from a T cell mediated immune reaction.

The Examiner further contends because Lederman discloses that 5c8 antibodies can be used for treating diabetes, Lederman discloses the present invention. However, this assertion is also incorrect. Lederman mentions diabetes can be treated by the disclosed method within a list of known B cell mediated diseases. There is no teaching or suggestion of the treating diabetes in the context of a T cell mediated autoimmune disorder. While it was known that diabetes has both B and T cell mediated components, there is nothing in the teachings or disclosure of Lederman to suggest his method can be used to treat the T cell mediated aspects of disease. Clark Declaration, ¶¶ 18 and 19. A more logical reading of Lederman by a person of skill in the art at the time of the application is that it implies that diabetes and transplant rejections, like the other listed B cell mediated diseases, can be treated by the 5c8 antibody. Thus, for this additional reason, Lederman does not teach the currently claimed invention of preventing T cell mediated tissue destruction associated with type I diabetes.

While conceding that Lederman only teaches B cell activation, the Examiner asserts that it was known in the art that "CD40L was expressed on important activated CD4+ T cells that regulated various immune responses and that CD40L was targeted in conditions and disorders known to be cell-mediated at the time the invention was made." *See* Final Office Action dated February 7, 2007, page 9 (emphasis added). The Examiner also states that the prior art teaches "the advantages of anti-CD40L antibodies to inhibit immune responses by targeting the CD40L

on T helper cells in therapeutic modalities of immunosuppression at the time the invention was made." *Id.* However, these statements do not support the contention that Lederman teaches a T cell mediated response in type I diabetes since the T cell mediated response involves autoreactive CD8+ cytoxic T cells, not CD4+ T helper cells. *See* Clark Declaration, ¶¶ 3 and 14. Thus, the disclosure of in the prior art that CD40L was expressed on helper T cells would not have lead a person of skill in the art to the claimed use of an anti-CD40L antibody in inhibiting a T cell mediated immune response because these helper T cells are not involved in this response. *See* Clark Declaration, ¶¶ 3, 12 and 14.

Additionally, Lederman does not even teach a person of skill in the art to treat the B cell mediated diseases because there are no data anywhere in Lederman showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. There are no data showing the effect of normal human T cells expressing what is called T-BAM on an immune response *in vitro* or *in vivo*. Lederman provides no evidence to establish that: (a) the 5c8 anti-CD40L monoclonal antibody binds to cells other than human T cells activated by non-physiologic stimuli and the Jurkat human T cell line; and (b) the 5c8 antibody can affect an autoimmune disease in an animal including humans. There are no functional data in Lederman using T cells activated with physiologic stimuli, *i.e.,* antigen, and no data assessing the role of an anti-CD40L antibody *in vivo* which would be essential to know if the antibody could inhibit autoimmune disease. *See* Clark Declaration, ¶¶ 20-24.

For the reasons set forth above, Lederman does not teach or suggest every limitation of the claims on appeal. Specifically, because Lederman only discloses a method for preventing B cell activation, there is no teaching or suggestion in the reference of a method for "preventing *T cell mediated tissue destruction associated with type I diabetes*.. wherein ... tissue destruction results from *a T cell mediated immune reaction to autoantigen.*" As will be discussed below, without a teaching or suggestion of the use of the 5c8 antibody to prevent a T cell mediated immune response, Lederman cannot render the claims on appeal obvious either alone or in combination with Noelle because one of skill in the art would not have reasonably considered that a gp39 antagonist could have been used to prevent a T cell mediated response. This is because at the time of filing the application, it was not known that gp39 had any involvement in T cell mediated immune responses independent of B cell activation.

2. Noelle does not Disclose or Suggest the Currently Claimed Invention

The present claims call for a method for preventing T cell mediated tissue destruction associated with type I diabetes comprising the administration of a gp39 antagonist, wherein the tissue destruction results from a T cell mediated immune reaction to an autoantigen. The Noelle '037 patent would not have lead a person of skill in the art to treat diabetes with anti-gp39 antagonists, either alone or in combination with other prior art. Noelle, while disclosing that a gp39 antagonist can induce antigen specific T cell tolerance when administered in conjunction with the antigen or antigen presenting cell (APC) to be tolerized, does not teach or suggest administering a gp39 antagonist alone to prevent T cell mediated autoimmune responses, much less tissue destruction associated with diabetes.

One skilled in the art at the time the present invention was made might have thought that this treatment may be pertinent for the treatment of diabetes to the extent that the method in Noelle involves pancreatic allografts (Clark Declaration, ¶ 17). However, this would not suggest that the underlying diabetes could be directly treated with an anti-gp39 antagonist alone, *i.e.*, without co-administration of an antigen, especially for disease not disclosed in the reference, and one where the antigen is not defined. In short, the Noelle '037 patent concerns the induction of antigen-specific T cell tolerance that would be applicable to allogeneic transplantation or autoimmune disease where the autoantigens are clearly defined. *See* Clark Declaration, ¶ 17.

Moreover, Noelle discloses that the induction of T cell tolerance to a specific antigen is in the context of T helper function and activation of B cells. *See* Noelle, col. 2, lines 46-52; col. 9, line 64-col. 10, line 5. As fully discussed below, the T cell mediated component of type I diabetes is T cell mediated destruction of beta cells, caused by autoreactive CD8+ cytotoxic T cells which are completely different than helper T cells and independent of B cell activation. Also, it was not known in June of 1995 that CD40L was expressed on cytotoxic or effector T cells in the pancreas, thus, the disclosure of pancreatic allografts in Noelle would not lead a person of skill in the art to believe that a gp39/CD40L antagonist could be used to prevent T cell mediated tissue destruction associated with diabetes. *See* Clark Declaration, ¶ 14.

Appellant has shown that the claims on appeal and the teachings of the prior art differ. Lederman teaches only the use of a gp39 antagonist to inhibit B cell mediated immune responses to treat diabetes. There is no disclosure or suggestion of the method of the claims on appeal where T cell mediated tissue destruction associated with type I diabetes caused by a T cell mediated immune reaction is prevented. Noelle discloses the use of a gp39 antagonist in combination with an antigen or an antigen presenting cell to treat transplantation rejection. There is no disclosure or suggestion in Noelle of the claimed method where a gp39 antagonist is administered alone to prevent the T cell mediated tissue destruction associated with type I diabetes caused by a T cell mediated immune reaction to an autoantigen. As will be shown below, in view of the knowledge in the art at the time of filing, these differences between the teachings of Lederman and Noelle, either alone or combined, and the presently claimed method are too great for a person of skill in the art to have considered the claimed method obvious at the time of filing.

3. There was no Motivation to Combine Lederman with Noelle and no Expectation of Success

There must be some motivation to combine references in order to make an obviousness rejection. The motivation must come from the prior art references themselves or the knowledge in the art. In this case, the Examiner has not shown any motivation for a person of skill in the art to combine Lederman and Noelle to obtain the invention of the claims on appeal.

There would have been no motivation to combine Lederman and Noelle because Lederman is concerned with the use of a gp39 antagonist alone to treat B cell mediated autoimmune disorders, and Noelle teaches the use of a gp39 antagonist administered with an antigen or antigen presenting cell to inhibit immune responses to donor antigens. There is no description or suggestion in Noelle to modify the method described therein to exclude the administration of donor antigen or donor antigen-expressing cells for the purpose of achieving an inhibition of a response to self, such as in autoimmune disorders. Additionally, there is no disclosure or suggestion in Noelle that a gp39 antagonist could be used to treat diabetes.

Also, there would have been no expectation of success in achieving the claimed method by combining the teachings of Lederman and Noelle. The claims on appeal call for the prevention of T cell mediated tissue destruction associated with type I diabetes caused by a T cell mediated immune reaction to an autoantigen. This T cell mediated tissue destruction is independent of B cell activation and caused by cytotoxic CD8+ T cells. Thus, a person of skill in the art would not have expected a method of preventing this T cell tissue destruction associated with type I diabetes using a gp39 antagonist to be successful from the combined teachings of the prior art as there is no disclosure or suggestion of the inhibition of cytotoxic T cell activation independent of B cell activation and at the time it was not known that gp39 had any involvement in this immune response.

4. The Knowledge and Level of Ordinary Skill in the Art in June of 1995

Appellant has also presented evidence as to the level of ordinary skill and knowledge in the art in June of 1995. The level of skill in the art at the time was a practitioner with a doctorate degree in immunology. The knowledge at this time was set forth in the Clark Declaration and accompanying literature. At this time, it was not recognized that gp39 had a role in non-B cell immune responses and any teaching of using an anti-gp39 antibody for blocking B cell mediated responses would not have suggested using an anti-gp39 antibody for blocking T cell mediated immune responses because these are two different immune responses.

T cells are divided into two broad categories, CD4+ T lymphocytes, which express the CD4 receptor ("helper" T cells) and CD8+ T lymphocytes, which express the CD8 receptor ("effector" or "cytotoxic" T cells). Immune responses are initiated by presentation of processed antigen by antigen-presenting cells (APCs) to T cells. Antigens are taken up by APCs and presented to T cells in association with either major histocompatibility complex (MHC) class I or class II molecules on the surface of the APC. CD4 binds class II MHC molecules, while CD8 binds class I MHC molecules. Peptides presented with class I molecules stimulate cytotoxic T cells to kill the cell from which the antigen was derived. In contrast, peptides presented with class II molecules stimulate helper T cells to generate further immune responses. Clark Declaration, ¶ 3.

There are two types of immune responses, humoral or B cell mediated, and cellular or T cell mediated. In humoral response, helper T cell stimulation of B cells leads to B cell activation, proliferation and differentiation into antibody-secreting cells. Humoral responses are characterized by the fact that the immune response can be transferred from one experimental animal to another by transfer of antigen-specific antibodies. Lederman discloses the inhibition of this helper T cell stimulation of B cells and the inhibition of the humoral response. Clark Declaration, ¶ 5.

In humoral responses, binding of antibodies to antigens can target an antigen for phagocytosis, leading to complement fixation and/or the attraction of inflammatory cells. This leads to cellular injury. An example of an antibody-mediated disease is systemic lupus erythematosis. Clark Declaration, ¶ 6.

In contrast to humoral immune responses, T cell mediated responses are not mediated by auto-antibodies, and represent an immune response independent of B cell activation. Immune responses of this type can be transferred in experimental disease models by the transfer of T cells as opposed to antibodies. Examples of T cell mediated autoimmune disorder models are EAE, a model for multiple scleroris, and the NOD mouse, which spontaneously develops insulitis and diabetes. Clark Declaration, ¶ 7, and Exhibits B and C to Clark Declaration.

Moreover, at the time of the invention, it was not known that gp39/CD40L had any involvement in non-B cell activation and immune responses. Clark Declaration, ¶ 9. In June of 1995, there were some reports of an anti-gp39 antagonist blocking B cell production of T cell dependent antibodies (Clark Declaration, ¶ 10; Exhibits D and E to Clark Declaration). However, at this time there were no published reports of the role of gp39/CD40L in regulating non-B cell immunity. In late 1995, some reports were starting to be published that showed a gp39 antagonist could, in certain situations, block T cell mediated resistance that did not involve B cells (Clark Declaration, ¶ 11; Exhibit F to Clark Declaration), however, in 1996, it was still uncertain if gp39/CD40L had any role in the T cell immune response (Clark Declaration, ¶ 11: Exhibit H to Clark Declaration).

The T cell mediated component of type I diabetes is the T cell mediated destruction of beta cells. In T cell mediated diabetic complications, autoreactive CD8+ cytotoxic T cells recognize peptides from a beta cell specific protein, bind to the beta cells, and selectively destroy these cells. This process occurs independently of any antibody response, because cytotoxic T cells are activated by APCs, which present the antigen to the T cells, and subsequently seek and destroy cells expressing antigen. Antibodies are not necessary for this response. Thus, a person of skill in the art would not have thought to use an anti-CD40L antibody to treat T cell mediated effects in diabetes because completely different T cells (cytotoxic versus helper) need to be targeted. Those of ordinary skill in the art would have not considered the destruction of beta cells by cytotoxic T cells, and inflammation cause by T cell mediated activation of other immune cells such as macrophages, to be treatable or preventable by the administration of a gp39/CD40L antagonist since it was not known that gp39/CD40L played a role in this type of T cell mediated immune response. Clark Declaration, ¶¶ 14 and 16.

The Examiner has countered this showing by arguing that the Applicant is relying upon mechanisms of action of the asserted teachings of the prior art and has not distinguished the expectation of success in treating a patient with diabetes with a gp39/CD40L/5c8 antagonist based upon the teachings of the prior art. *See* Final Office Action dated February 6, 2007, page 7. Appellant respectfully submits it is more than a difference in mechanism of action that distinguishes the present invention over the teachings of the prior art. The treatment of "tissue damage [that] results from a T cell mediated immune reaction to an autoantigen" by a patient with type I diabetes as currently claimed is different than treating tissue damage resulting from B cell mediated immune reactions. It involves treating inflammation and destruction of beta cells by macrophages and cytotoxic T cells, not autoantibodies. As shown, this type of T cell mediated tissue damage was not considered treatable by gp39 antagonists in June of 1995. *See* Clark Declaration, ¶¶ 14 and 16.

The first study even suggesting CD40L-CD40 interactions in T cell-mediated aspects of diabetes was published almost a year and half after the filing date of the present application in November of 1997. The authors of the study stated that while CD40-CD40L interactions in B cell mediated autoimmune disease had been reported, the possibility that CD40-CD40L

interactions play a role in T cell dependent autoimmune disease "remains untested." *See* Exhibit K to Clark Declaration, page 4620, *see also* Clark Declaration, ¶ 15.

Thus, Appellant has shown through the Clark Declaration and the attached literature (which exemplifies the art at the time the present application was filed), that at time of filing the current application, it was not known if gp39 had any role in non-B cell immune responses, especially those associated with type I diabetes, *i.e.*, cytotoxic T cells. Without an express disclosure or suggestion in the combined teachings of the prior art of the use of a gp39 antagonist to prevent T cell mediated tissue destruction associated with type I diabetes wherein tissue destruction results from a T cell mediated immune reaction to an autoantigen, the claims on appeal would not have been obvious to a person of skill in the art at the time of the application.

5. Evidence of Unexpected Results

The Appellant has also submitted evidence of unexpected results that has not been properly considered by the Examiner. As shown in the discussion regarding the knowledge in the art in June of 1995, it clearly can be seen that B cell, *i.e.*, humoral, and T cell, *i.e.*, cellular, mediated immune responses have completely different mechanisms of action. Thus, the disclosure of the current application provides an entirely unexpected result, specifically, that inhibition of a T cell receptor previously shown to be necessary for the disruption of T cell-B cell interactions only, is capable of inhibiting the symptoms and/or progression of an autoimmune disease that is non-B cell mediated, *i.e.*, T cell mediated. This unexpected use of a gp39 antagonist to prevent T cell mediated tissue destruction associated with type I diabetes wherein the tissue destruction results from a T cell mediated immune reaction to an autoantigen is covered in all of the claims on appeal.

At the time of the invention, one of skill in the art would not have recognized that a gp39 antagonist would have an effect a disease or tissue destruction caused by a T cell mediated immune reactions because that mechanism of disease or destruction is independent of B cell activation, which was considered the primary role of gp39. It was not known in the art in June of 1995 that gp39 had any role in non-B cell immune responses. *See* Clark Declaration, ¶ 9.

Autoimmune diseases are often the products of both B cell and T cell mediated responses. But while it would have been expected in June of 1995 to successfully treat the B cell/humoral/antibody-mediated responses using an anti-gp39 antagonist which interferes with the helper T cell-B cell interactions, it would have not been expected that the same method would be useful to treat T cell mediated aspects of autoimmune disease and T cell mediated tissue destruction caused by cytotoxic T cells. *See* Clark Declaration, ¶¶ 9-16. In June of 1995, gp39 was thought to be involved in only T cell- B cell interactions. Its potential role in non-B cell immune responses was only elucidated after the filing date of the present application. More importantly, *the role of gp39 in the T cell mediated aspects of diabetes remained untested and unknown at least a year after the filing date of the present application.* Thus, one of skill in the art would not have been lead to the presently claimed invention of using an anti-gp39 antibody to treat T cell-mediated tissue destruction in diabetes based upon the teachings of Lederman in combination with Noelle of antagonists of the helper T cell-B cell interaction. There was simply not enough knowledge in the art at the time. Indeed, the state of the art would have lead a person of skill to the correct conclusion that Lederman only teaches the use of an anti-gp39 antibody in the treatment of B cell-mediated autoimmune disease, and that alone or in combination with Noelle, there is no suggestion of the currently claimed method. Thus, the success of the method of the present invention in treating T cell-mediated tissue destruction is unexpected in light of the knowledge in the art in June of 1995.

Additional evidence of unexpected results of a method of using the 24-31 antibody as in the claims on appeal was submitted with an Amendment dated April 1, 2005. Exhibit B to this Amendment, Vincenti (2002) American Journal of Transplantation, 2:898-903, discloses that hu5c8, the humanized 5c8 antibody disclosed in Lederman, caused thromboembolic events as well as failing to efficiently suppress the immune response. *See* Vincenti, page 899. In contrast, the 24-31 antibody used in the claimed method was found therapeutically safe (see Exhibit C to the Amendment dated April 1, 2005). Lastly, the Declaration of Randolph Noelle sets forth that (1) the 5c8 and 24-31 antibodies bind to different epitopes on gp39; (2) while the two antibodies have similar binding affinity, the 5c8 has a slightly better affinity; (3) the 24-31 antibody inhibits binding of gp39 more effectively than 5c8; and (4) the 24-31 antibody inhibits the biological

function of gp39 substantially better (about 3-fold) than 5c8. See Exhibit D to Amendment dated April 1, 2005, page 6.

This evidence clearly shows superior unexpected results of a method using the 24-31 antibody as opposed to the Lederman 5c8 antibody. Not only is the 24-31 antibody more effective in preventing unwanted immune responses mediated by gp39, it is also therapeutically safer. These unexpected advantages could not have been predicted by the teachings of Lederman in combination with Noelle. This evidence was not accorded its due weight by the Examiner.

VIII. Conclusion

For the foregoing reasons the Examiner's rejection of the pending claims should be reversed.

Dated: January 7, 2008

Respectfully submitted,

By _____

Bonnie Kramer Carney
Registration No.: 36,073
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

CLAIMS APPENDIX

1. (Rejected) A method for preventing T cell mediated tissue destruction associated with type 1 diabetes comprising administering to a subject in need of such treatment a prophylactically effective amount of a gp39 antagonist selected from the group consisting of soluble CD40, CD40 fusion protein, and an anti-gp39 antibody, or a fragment thereof that binds gp39, wherein the anti-gp39 antibody is produced by 24-31 hybridoma, ATCC Accession Number HB 11712, and tissue destruction results from a T cell mediated immune reaction to an autoantigen.

2-4. (Canceled).

5. (Rejected) The method of claim 1, wherein the gp39 antagonist is an anti-gp39 antibody.

6. (Rejected) The method of claim 5, wherein the anti-gp39 antibody is a monoclonal antibody.

7. (Rejected) The method of claim 5, wherein the anti-gp39 antibody is an anti-human gp39 antibody.

8. (Rejected) The method of claim 6, wherein the monoclonal antibody is 24-31.

9. (Rejected) The method of claim 6, wherein the monoclonal antibody is a chimeric monoclonal antibody containing constant regions and variable regions from different species.

10. (Rejected) The method of claim 6, wherein the monoclonal antibody is a humanized monoclonal antibody.

11.-16. (Canceled).

17. (Rejected) The method of claim 9, wherein the chimeric monoclonal anti-gp39 antibody comprises a variable region of monoclonal antibody 24-31.

18. (Canceled).

19. (Rejected) The method of claim 10, wherein the humanized monoclonal anti-gp39 antibody comprises a hypervariable region of monoclonal antibody 24-31.

20-21. (Canceled).

EVIDENCE APPENDIX

Appellant is relying upon the following evidence of record:

1. Vincenti (2002) American Journal of Transplantation, 2:898-903 (Exhibit B to Amendment dated April 1, 2005);

2. Results of Clinical Trials with IDEC 131 (Exhibit C to Amendment dated April 1, 2005);

3. Declaration under 37 C.F.R. § 1.132 of Randolph Noelle, Ph.D. (Exhibit D to Amendment dated submitted April 1, 2005).

These three documents were entered into the record by the Examiner in his Official Action dated June 16, 2005.

4. Declaration under 37 C.F.R. § 1.132 of Edward A. Clark, Ph.D. and Exhibits A-M attached therein. The Clark Declaration was submitted with the Amendment and Response dated November 6, 2006. This document was entered into the record by the Examiner in his Official Action dated February 7, 2007.

RELATED PROCEEDINGS APPENDIX

None